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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/477,147	06/07/1995	PHILIP O. LIVINGSTON	43016-D/JPW/	5687

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[REDACTED] EXAMINER

HOLLERAN, ANNE L

[REDACTED] ART UNIT [REDACTED] PAPER NUMBER

1642

DATE MAILED: 12/31/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>
	08/477,147	LIVINGSTON ET AL.
	<b>Examiner</b>	<b>Art Unit</b>
	Anne Holleran	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 07 October 2002.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 109-122 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 109-122 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                    | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____                                    |

**DETAILED ACTION**

1. The amendment October 7, 2002 is acknowledged. Claim 109 was amended.
2. Claims 109-122 are pending and examined on the merits.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Objections / Rejections Maintained:***

4. Claims 109-122 are provisionally rejected under the judicially created doctrine of obviousness-type, double patenting as being unpatentable over the claims 78, 80-92, 94 and 96-99 of copending Application No. 08/477,097 for reasons already made of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because they all claim conjugates and methods of using said conjugates, where the conjugate comprises a ganglioside conjugated to a protein through the ceramide portion. Thus, the particular species drawn to GM2 or GD2 claimed in the copending application would anticipate the instant genus composition claims.

Applicant argues that the provisional rejection should be allowed to drop and that the instant claims be allowed to issue, pursuant to MPEP section 804. Since the instant claims are not allowable, the provisional double patenting rejection is maintained for the reasons of record.

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5. Claims 109-122 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 78-93 and 95-100 of copending Application No. 08/475,784 for reasons already made of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because they all claim conjugates where the conjugate comprises a ganglioside conjugated to a protein through the ceramide portion by means of conjugating proteins to gangliosides through the ceramide portion. Thus, the particular species claimed in the copending application would anticipate the instant genus composition claims.

Applicant argues that the provisional rejection should be allowed to drop and that the instant claims be allowed to issue, pursuant to MPEP section 804. Since the instant claims are not allowable, the provisional double patenting rejection is maintained for the reasons of record.

6. Claims 109-122 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 97, 101-111 and 113-118 of copending Application No. 08/196,154 for reasons already made of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because they claim conjugates, and methods of using said conjugates, where the conjugate comprises a ganglioside conjugated to a protein through the ceramide portion. Thus, the GM2 species claimed in the copending application would anticipate the instant genus composition claims.

Applicant argues that the provisional rejection should be allowed to drop and that the instant claims be allowed to issue, pursuant to MPEP section 804. Since the instant claims are not allowable, the provisional double patenting rejection is maintained for the reasons of record.

***Claim Rejections Withdrawn:***

7. The rejection of claims 78-92, 94 and 96-99 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in view of the amendment.
8. The rejection of claims 78-92, 94 and 96-99 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research, 149:7045-7050, 1989) in view of Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (Immunobiol, 182:32-43, 1990), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), and Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976) is withdrawn in view of the amendment.

***New Grounds of Rejection:***

9. Claims 109-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiegand et al (U.S. Patent 5,599,914; issued Feb. 4, 1997; filed Nov. 24, 1989) in view of Fiume et al (Critical Rev. Therapeutic Drug Carrier Systems, 4(4): 265-284, 1988), Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), and Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976).

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Wiegand discloses modified glycosphingolipids (GM3, GD3, GM2 and GM1). Wiegand discloses a method for chemical modification of the sphingoid portions of glycosphingolipids to make glycosphingolipids capable of coupling to proteins (see abstract). Wiegand discloses that the method of chemical modification is that of ozonolysis at the C-4 double-bond of the sphingosine base resulting in the formation of a reactive aldehyde species (col. 2, line 43 - col. 3, line 67). Wiegand discloses that the aldehyde group is susceptible to reductive amination. Wiegand fails to disclose conjugation of the modified glycosphingolipid to KLH via an amine linkage between the C-4 carbon of sphingosine base and an  $\epsilon$ -aminolysyl group of KLH. Wiegand also fails to disclose a composition that comprising a saponin derivable from the bark of the Quillaja saponaria Molina Tree (QS-21).

Fiume (1988) teaches that reductive amination of reactive aldheyde species with proteins having  $\epsilon$ -lysine groups is well known in the art (see page 268-269). Specifically, Fiume teaches that aldehyde group of a galactosyl residue may be reacted with an  $\epsilon$ -lysine of a protein.

Ritter (1991) teaches that IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response (page 406, paragraph 1). Ritter teaches that the advantage of inducing an IgG antibody response (vs IgM) against gangliosides is that IgG: a) has a higher affinity, b) is better able to penetrate solid tissues, c) is able to mediate antibody-dependent cell-mediated cytotoxicity, d) and is generally detectable in the serum for longer periods after immunization.

Kensil et al teach that QS-21 (i.e. the instant carbohydrate derivable from the bark of a Quillaja saponaria Molina tree) produced a higher antibody response than conventional aluminum hydroxide (page 433, column 2, paragraph 4, and Figure 3). Kensil et al also teach that

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the immune responses obtained with QS-21, reached a plateau at doses between 10-80 ug in mice (page 433, column 1, paragraph 3).

Maricani et al teach the use of QS-21 adjuvant was useful because it did not cause a toxic reaction in cats (page 93, paragraph 1).

Uemura et al (J Biochem, 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptic reactivity of the ganglioside derivative with antibodies.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the modified glycosphingolipids of Wiegand to make glycoconjugates that are the same as those claimed. Weigand teaches a modified glycosphingolipid that has a reactive aldehyde group (at the C-4 position of the sphingosine base) that may be used for coupling to proteins as taught by Fiume, because Fiume demonstrates that methods of reductive amination to link proteins, via  $\epsilon$ -lysine residues, to reactive aldehyde groups is known in the art. Because Wiegand teaches a method of ozonolysis that results in the formation of a reactive aldehyde species, the bond that would be formed between the C-4 carbon of the sphingosine base and the KLH would be an amino linkage that would cause the C-4 carbon to be present in a  $\text{CH}_2$  group. It would have been further prima facie obvious to one of ordinary skill in the art to have used KLH as the protein carrier because, as Ritter teaches, attachment of gangliosides to carrier proteins such as KLH increase IgG responses to gangliosides. It would have been prima facie obvious to one of ordinary skill in the art to add QS-21, because, as taught by Kensil, it provides for a higher antibody response, and QS-21 provides the advantages that it is not toxic to animals (see Marciani).

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It also would have been *prima facie* obvious to optimize the doses of QS-21 in the composition, also it would have been *prima facie* obvious to one of ordinary skill in the art to optimize the weight ratio of the components of the composition to provide an optimal response.

One would have reasonably expected the conjugation procedure to work as substituted because conjugation through the e-aminolysyl groups of carrier proteins for enhance immunogenicitiy is routine in the art and, as Uemura (1976) teaches, ozonolysis and reduction of various sphingolipids does not affect the haptenic reactivity with antibodies.

### *Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran  
Patent Examiner  
December 30, 2002

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